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April 1981

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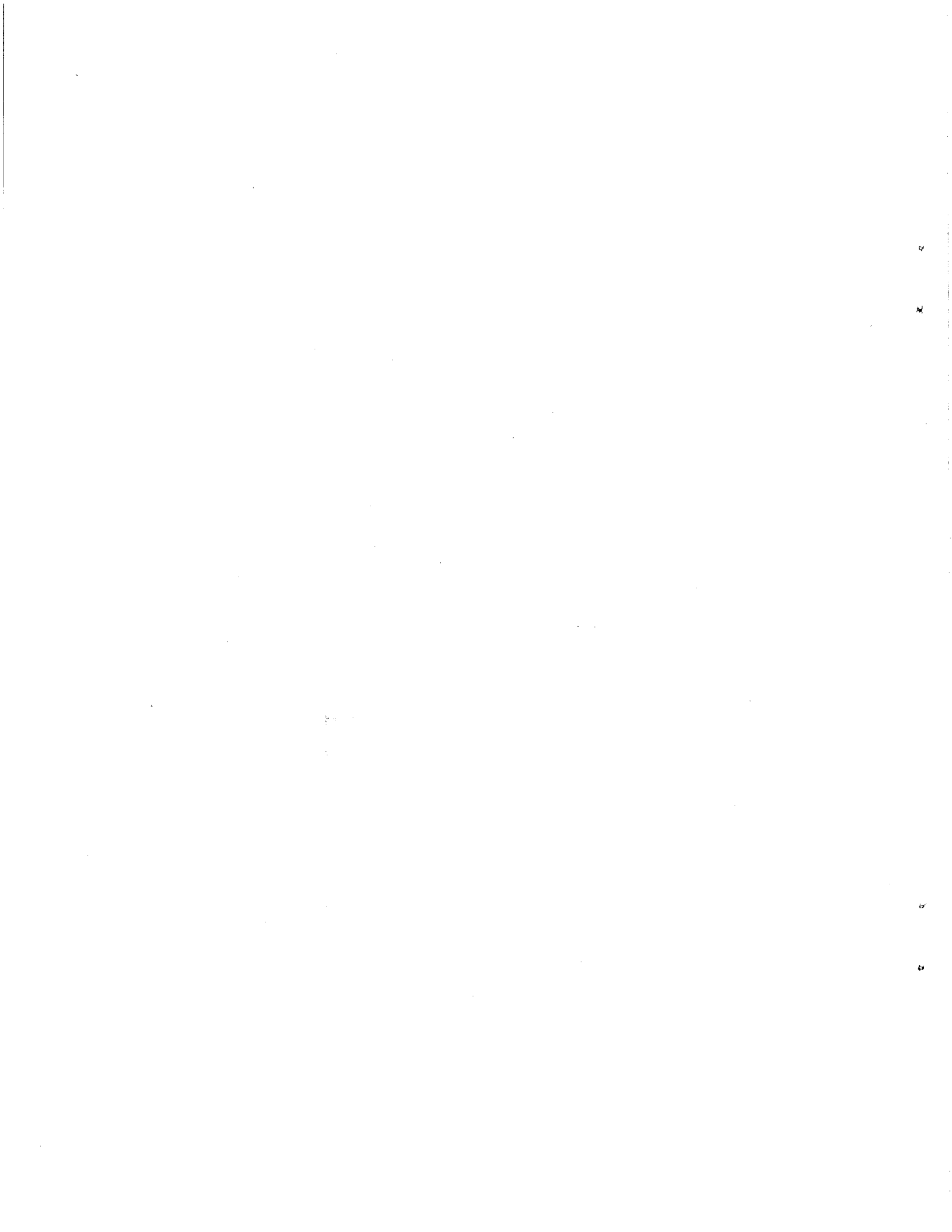
RISK ESTIMATION AND DECISION-MAKING:  
IMPLICATIONS OF THE 1980 BEIR-III REPORT<sup>1,2</sup>

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## INTRODUCTION

My assignment today is to try to give some sort of general background of the implications the current Report<sup>1</sup> of the Committee on the Biological Effects of Ionizing Radiation, National Academy of Sciences-National Research Council (The BEIR-III Report) may have on societal decision-making in the regulation of activities concerned with the health effects of low-level radiation (Table 1). I shall try to discuss how certain of the areas addressed by the present BEIR Committee attempt to deal with the scientific basis for establishing appropriate radiation protection guides, and how the Report<sup>1</sup> may not necessarily serve as a comprehensive review and evaluation of existing scientific knowledge concerning low-level radiation exposure to human populations. Whatever I may consider important in these discussions, I speak only as an individual, and in no way do I speak for the BEIR Committee whose present deliberations are soon to become available. It would be difficult for me not to be somewhat biased and directed in favor of the substance of the BEIR Reports<sup>1-3</sup>, since as an individual I have been sufficiently close to the ongoing scientific deliberations of agreement and disagreement as they developed over the past 10 years.

I think the best thing for one to do is to discuss very briefly why we have advisory committees on radiation, and why the BEIR Committee, and its current Report<sup>1</sup>, may be somewhat different than the others. To do this, I shall review what we know and what we do not know about the health effects of low-level radiation, particularly as these may highlight the controversy which has led to scientific dispute within the Committee. Further, I shall comment on how the risks of radiation-induced cancer in man have been

estimated, the sources of the epidemiological data, the dose-response models used, and the uncertainties which limit precision of estimation of excess risks from radiation. And finally, I should like to conjecture with you on what lessons we have learned or should have learned from the BEIR-III Committee experience, and especially on what the implications might be of numerical risk estimation for radiation protection and public health policy.

#### WHY DO WE HAVE ADVISORY COMMITTEES ON RADIATION?

For more than half a century, responsible public awareness of the potential health effects of ionizing radiations from medical and industrial exposure, from nuclear weapons and weapons testing, and from the production of nuclear energy has called for expert scientific advice and guidance. And, advisory committees on radiation of national and international scientific composition have for these many years met and served faithfully and effectively to deliberate and to report on three important matters of societal concern (Table 2): (1) to place into perspective the extent of harm to the health of man and his descendants to be expected in the present and in the future from those societal activities involving ionizing radiations; (2) to develop quantitative indices of harm based on dose-response relationships in order to provide a scientific basis to be applied to concepts of acceptable risk and protection of human populations exposed to radiation related primarily to somatic and genetic risks; (3) to identify the extent of radiation activities which could cause harm, to assess their relative significance, and to provide a framework on how to reduce unnecessary radiation exposure to human populations.

To a greater or lesser extent, each advisory committee on radiation---such as the UNSCEAR, the ICRP, the NCRP, and the BEIR Committee---have dealt extensively with these matters. But significant differences occur in the scientific reports of these various bodies, and we should expect differences to occur, because of the charge, the scope, and the composition of each Committee, and most important, public attitudes existing at the time of the deliberations of that particular committee, and at the time of the writing of that particular report. The BEIR Report<sup>1</sup> is different; however, the main difference is not so much from new data or new interpretations of existing data, but rather from a philosophical approach and appraisal of existing and future radiation protection resulting from an atmosphere of constantly changing societal conditions and public attitudes.

#### WHY IS THE BEIR REPORT<sup>1</sup> DIFFERENT?

The Report<sup>1</sup> of the Committee on the Biological Effects of Ionizing Radiations of the National Academy of Sciences-National Research Council is the record of the deliberations of a standing expert scientific advisory committee (the BEIR Committee) and deals with the scientific basis of the health effects in human populations exposed to low levels of ionizing radiation. The current Report<sup>1</sup> broadly encompasses two areas (Table 3): (1) it reviews the current scientific knowledge---epidemiological surveys and laboratory experiments---relevant to radiation exposure of human populations and the delayed or late health effects of low-level radiation; (2) it evaluates and analyzes these late health effects---both somatic and genetic effects---in relation to the risks from exposure to low-level radiation. The BEIR Committee is an advisory committee

to the National Academy of Sciences-National Research Council. It presently consists of 22 members, selected for their special scientific expertise in areas of biology, biophysics, biostatistics, epidemiology, genetics, mathematics, medicine, physics, public health, and the radiological sciences. The reports<sup>1-3</sup> of this advisory committee have, in the past, become a reference text as a scientific basis for the development of appropriate and practical radiation protection standards.

The 1972 BEIR-I Report<sup>2</sup> and the forthcoming BEIR-III Report<sup>1</sup> differ from one or more of the other radiation advisory committee reports of the UNSCEAR<sup>4,5</sup>, the ICRP<sup>6,7</sup>, the NCRP<sup>8,9</sup>, and of other national councils and committees, in four important ways (Table 4):

(1) The BEIR Report<sup>1-3</sup> is intended to be a readable, usable document for all activities concerned with radiation health. The conclusions, recommendations, and scientific appendices are purposefully written in a straightforward manner, to be read and understood by physicists and physicians, by congressmen and counsellors, by unions and utilities, and by engineers and environmentalists.

(2) The BEIR Report<sup>1-3</sup> does not set radiation standards or public health policy. However, the Report<sup>3</sup> is purposefully presented so that it will be useful to those responsible for decision-making concerning regulatory programs and public health policy involving radiation in the United States. There is no intent to make the task any easier or to set a firm direction for those decision-makers who must take into account those considerations of science and technology, the relevant societal and economic matters, and the development and execution of such regulatory programs. In this regard, the BEIR Report<sup>3</sup> suggests that those responsible for setting radiation protection



standards must always take into account societal needs at that time, so that such standards are established on levels of radiation exposure which are not necessarily absolutely safe, but rather those which are considered to be appropriately safe for existing circumstances at the time to fulfill society's needs, particularly in the areas of general population and occupational exposure from medical radiation and nuclear energy.

(3) The experimental data and epidemiological surveys are carefully reviewed and assessed for their value in estimating numerical risk coefficients for the health effects in human populations exposed to low-level radiation. Such deliberations require scientific judgment and assumptions based on the available epidemiological and experimental data only, and have necessarily and understandably led to disagreement not only outside the committee room, but among committee members as well. But such dispute and disagreement center not on the scientific facts and not on the existing epidemiological and experimental data, but rather on the assumptions, interpretations, and analyses of the available facts and data. Therefore, the BEIR Report<sup>3</sup> uses a particularly practical format for decision-makers, namely, the numerical risk coefficients estimated are presented in probabilistic terms, within most likely upper and lower boundaries, derived solely from the scientific facts, the epidemiological data, and the scientific hypotheses and assumptions on which they are based.

(4) The BEIR Report<sup>1-3</sup> addresses the continued need to assess and evaluate the benefits from those activities involving radiation as well as the risks. In our resource-limited society, such benefit-risk assessment is essential for societal decision-making for establishing appropriate and achievable radiation protection standards. Decisions can and must be made

on the value and costs of technological and societal programs for the reduction of risk by reducing the levels of radiation exposure. This would include societal choices centered as well on alternative methods involving nonradiation activities available through a comparison of the costs to human health and to the environment<sup>3</sup>.

#### WHAT ARE THE IMPORTANT BIOLOGICAL EFFECTS OF LOW-LEVEL RADIATION?

My remarks here will be restricted primarily to those delayed or late health effects in humans following exposure to low-LET radiation, x-rays and to gamma rays from radioactive sources, and to a much lesser extent to high-LET neutron and alpha radiations, since these are the ionizing radiations most often encountered in medicine and in the nuclear industry. Briefly, low-level radiation can affect the cells and tissues of the body in three important ways (Table 5). First, if the macromolecular lesion occurs in one or a few cells, such as these of the hematopoietic tissues, the irradiated cell can occasionally transform into a cancer cell, and after a period of time, there is an increased risk of cancer developing in the exposed individual. This biological effect is called carcinogenesis; and the health effect, cancer. Second, if the embryo or fetus are exposed during gestation, injury can occur to the proliferating and differentiating cells and tissues, leading to abnormal growth. This biological effect is called teratogenesis; and the health effect, developmental abnormality in the newborn. Third, if the macromolecular lesion occurs in the reproductive cell of the testis or the ovary, the hereditary genome of the germ cell can be altered, and the injury can be expressed in the

descendants of the exposed individual. This biological effect is called mutagenesis; and the health effect, genetically-related ill-health.

There are a number of other biological effects of ionizing radiation, such as cataracts of the lens of the eye, or impairment of fertility, but these three important late effects---carcinogenesis, teratogenesis and mutagenesis---stand out as those of greatest concern. This is because a considerable amount of scientific information is known from epidemiological studies of exposed human populations and from laboratory animal experiments. Furthermore, we believe that any exposure to radiation, even at very low levels of dose, carries some risk of such deleterious effects. And, as the dose of radiation increases above very low levels, the risk of these deleterious health effects increases in exposed human populations. It is these latter observations that have been central to the public concern about the potential health effects of low-level radiation, and to the task of establishing standards for protection of the health of exposed populations. Indeed, all reports of expert advisory committees on radiation are in close agreement on the broad and substantive issues of such health effects.

#### WHAT DO WE KNOW ABOUT THE HEALTH EFFECTS OF LOW-LEVEL RADIATION?

A number of very important observations on the health effects of low-level radiation have now convincingly emerged, and about which there is firm general agreement (Table 6). These observations are based on careful statistical evaluation of epidemiological surveys of exposed human populations, in conjunction with extensive research in laboratory animals, and on analysis of dose-response relationships of carcinogenic, teratogenic and genetic effects,

and on known mechanisms of cell and tissue injury in vivo and in vitro.

1) Cancer induction is considered to be the most important late somatic effect of low-dose ionizing radiation. Solid cancers arising in the various organs and tissues, such as the female breast and the thyroid gland, rather than leukemia, are the principal late effects in individuals exposed to radiation. The different organs and tissues vary greatly in their relative susceptibility to cancer induction by radiation. The most frequently occurring radiation-induced cancer in man include, in decreasing order of susceptibility (Table 6): the female breast; the thyroid gland, especially in young children and in females; the hematopoietic tissues; the lung; certain organs of the gastrointestinal tract; and the bones. There are influences, however, of age at the time of irradiation, of sex, and of the radiation factors and types---LET and RBE---affecting the cancer risk.

2) The effects on growth and development in the irradiated embryo and fetus are related to the gestational stage at which exposure occurs. It appears that a threshold level of radiation dose may exist below which gross teratogenic effects will not be observed. However, these dose levels would vary greatly depending on the particular developmental abnormality.

3) It has been necessary to estimate genetic risks based mainly on laboratory mouse experiments because of the paucity of data from exposed human populations. Our knowledge of fundamental mechanisms of radiation injury at the genetic level is far more complete, thereby permitting greater assurance in extrapolating from laboratory experiments to man. Mutagenic effects are related linearly to radiation dose, even at very low levels of exposure. With new information on the broad spectrum and incidence of genetically-

related ill-health in man, such as mental retardation and diabetes, the risk of radiation mutagenesis in man affecting future generations takes on new and special consideration.

#### WHAT DO WE NOT KNOW ABOUT THE HEALTH EFFECTS OF LOW-LEVEL RADIATION?

In spite of a remarkable understanding of the health effects in exposed human populations, there is still a considerable amount we do not know about the potential health hazards of low-level radiation (Table 7):

1. We do not know what the health effects are at dose rates as low as a few hundred millirem per year. It is probable that if any health effects do occur, they will be masked by environmental or other competing factors that produce similar effects.

2. The vast epidemiological data on exposed human populations are nevertheless highly uncertain in regard to the forms of the dose-response relationships for radiation-induced cancer in man. This is especially the case for low-level radiation. Therefore, it has been necessary to estimate human cancer risk at low doses primarily from observations at relatively high doses, frequently greater than 100 rads and more. However, it is not known whether the cancer incidence observed at high dose levels also applies to cancer induction at low dose levels.

3. We have no reliable method at the present time of estimating the repair of injured cells and tissues of the body exposed to very low doses and dose rates. And further, we do not know how to identify those persons who may be particularly susceptible to radiation injury.



4. Analyses of the numerous epidemiological surveys of irradiated populations exposed in the past demonstrate that we have very limited information on the precise radiation doses absorbed by the tissues and organs. Furthermore, we do not know the complete cancer incidence in each study population, since new cases of cancer continue to appear with the passing of time. Accordingly, any estimation of excess cancer risk based on such limited dose-response information must necessarily be incomplete, until the entire study population has died from natural causes.

5. We do now know the role of competing environmental and other host factors---biological, chemical, or physical factors---existing at the time of exposure, or following exposure, which may influence and affect the carcinogenic, teratogenic, or genetic effects of low-level radiation.

#### WHAT ARE THE UNCERTAINTIES IN THE DOSE-RESPONSE RELATIONSHIPS FOR RADIATION-INDUCED CANCER?

The present BEIR-III Committee, in its earliest deliberations, recognized that there was great uncertainty in regard to the shapes of the dose-response curves for cancer induction by radiation in humans, and this was especially the case at low levels of dose. Estimates of excess cancer risk at low doses appear to depend more on what is assumed about the mathematical form of the dose-response function than on the available epidemiological data. Accordingly, in estimating the excess cancer risk from low-dose low-LET radiation, the BEIR-III Committee chose to use a linear-quadratic dose-response model felt to be consistent with epidemiological and radiobiological data in preference to more extreme dose-response models. In this regard, the current BEIR-III

Report<sup>1</sup> differs substantially from the 1972 BEIR-I Report<sup>2</sup>. I should like to examine the deliberations of this decision more closely.

In recent years, a general hypothesis for estimation of excess cancer risk in irradiated human populations, based on theoretical considerations, extensive experimental animal studies and epidemiological surveys, suggests that complex dose-response relationships between radiation dose and observed cancer incidence<sup>10-15</sup>. Perhaps the most widely accepted model for cancer induction by radiation, based on the available information and consistent with both knowledge and theory, takes the complex linear-quadratic form:  $I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2) \exp(-\beta_1 D - \beta_2 D^2)$ , where  $I$  is the cancer incidence in the irradiated population at radiation dose  $D$  in rad, and  $\alpha_0$ ,  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$  and  $\beta_2$  are non-negative constants (Figure 1). The multicomponent dose-response curve contains (1) an initial upward-curving linear and quadratic functions of dose which represents the process of cancer induction by radiation; and (2) a modifying exponential function of dose which represents the competing effect of cell killing at high doses.  $\alpha_0$  is the ordinate intercept at 0 dose, and defines the natural incidence of cancer in the population.  $\alpha_1$  is the initial slope at 0 dose, and defines the linear component in the low dose range.  $\alpha_2$  is the curvature near 0 dose, and defines the upward-curving quadratic function of dose.  $\beta_1$  and  $\beta_2$  are the slopes of the downward-curving function in the high dose range, and define the cell killing function.

Analysis of a large number of dose-incidence curves for cancer induction in irradiated populations, both in humans and in animals, has demonstrated that for different radiation-induced cancers only certain of the parameter values of these constants can be theoretically determined. However, the

extent of the variations in the shapes of the dose-response curve does not permit direct determination from the data of any of these parameter values with precision, or of assuming their values, or of assuming any fixed relationship between two or more of these parameters. In the case of the epidemiological surveys of irradiated human populations, this complex multicomponent general dose-response form cannot be universally applied. Therefore, it has become necessary to simplify the model by reducing the number of parameters which would have the least effect on the form of the dose-response relationship in the dose range of low-level radiation. Such simpler models, with increasing complexity, include the linear, quadratic, linear-quadratic, and finally, the multicomponent linear-quadratic form with an exponential modifier (Figure 2).

The BEIR-III Committee recognized three compelling situations which seriously limit precise numerical estimation of the excess cancer risk of low-level radiation in human populations (Table 8). (1) We lack an understanding of the fundamental mechanisms of cancer induction by radiation in man. (2) The dose-response information from human data is highly uncertain, particularly at low levels of dose. (3) Experimental and theoretical considerations suggest that various and different mathematical forms of dose-response relationships may exist for different radiation-induced cancers in exposed human populations. Nevertheless, these limitations do not relieve decision-makers of the responsibility for determining public health policy based on appropriate radiation protection standards. Accordingly, not only did the BEIR-III Committee consider it essential that quantitative risk estimation be determined, based on the available epidemiological and radiobiological data, but that in addition, it was equally essential that precise explanations and qualifications of the

assumptions and procedures involved in the determination of such risk estimates are to be provided. This has been done explicitly in the current BEIR-III Report<sup>1</sup> containing the estimates of excess cancer risk. The Committee recognized that some experimental and human data, as well as theoretical considerations, suggest that for exposure to low-LET radiation, such as x-rays and gamma rays, at low doses, the linear model probably leads to overestimates of the risk of most radiation-induced cancers in man, but that the model can be used to define the upper limits of risk. Similarly, the Committee believes that the quadratic model may be used to define the lower limits of risk from low-dose low-LET radiation. For exposure to high-LET radiation, such as neutrons and alpha particles, linear risk estimates for low doses are less likely to overestimate risk and may, in fact, underestimate risk.

#### WHAT IS THE CONTROVERSY OVER LOW-LEVEL RADIATION?

The estimation of the cancer risk of exposure to low-level radiation is said to be clouded by scientific dispute. In particular there appears to be disagreement among some scientists as to the effects of very low levels of radiation, even as low as our natural radiation background. While there is no precise definition of low-level exposure, most scientists would generally agree that low-level radiation is that which falls within the dose range considered permissible for occupational exposure. According to accepted standards<sup>16</sup>, 5 rem per year to the whole body would be an allowable upper limit of low-level radiation dose for the individual radiation worker.

In this context, and with this as the boundary condition for occupational exposure, then it could very well be concluded that most of the estimated

delayed cancer deaths which may be associated with a so-called hypothetical nuclear reactor accident, for example, are therefore considered by some scientists to be caused by exposures well below the allowable occupational limits. Furthermore, if it is assumed that any extra radiation above natural background, however small, causes additional cancer, then if millions of people are exposed, some extra cancers will inevitably result. Other scientists strongly dispute this, and firmly believe that low-level radiation is nowhere near as dangerous as their adversarial colleagues would insist. Central to this dispute, it must be remembered that cancers induced by radiation are indistinguishable from those occurring naturally; hence, their existence can be inferred only on the basis of a statistical excess above the natural incidence. Since such health effects, if any, are so rarely seen under low-level radiation because the exposures are so small, the issue of this dispute may never be resolved---it may be beyond the abilities of science and mathematics to decipher.

It is just this type of controversy that was at the root of the division within the present BEIR-III Committee. There is little doubt that the Committee's most difficult task has been to estimate the carcinogenic risk of low-dose low-LET whole-body radiation. Here, emphasis was placed almost entirely on the human epidemiological studies, since it was felt that little information from animal studies could be applied directly to man. Therefore, as the earlier 1972 BEIR-I Report<sup>2</sup> had done, some members of the present BEIR-III Committee chose it necessary to adopt a linear hypothesis of dose-response to estimate the cancer risk at very low-level radiation exposure where no human epidemiological data are available. Here, it was assumed the same proportional risks are present at low levels as at high levels of radiation. This position



implies that even very small doses of radiation are carcinogenic, a finding that could force the Environmental Protection Agency to adopt stricter health standards to protect against occupational and general population exposure. Other members of the Committee do not accept this position, and believe this is an alarmist approach. When there is no human epidemiological evidence at low doses, these scientists prefer to assume that the risks of causing cancer are proportionally lower.

Let us look at some of the problems. In its deliberations, the present BEIR-III Committee concluded two important points: (1) It is not yet possible to make precise low-dose estimates for cancer induction by radiation because the level of risk is so low that it cannot be observed directly. (2) There is great uncertainty as to the dose-response function most appropriate for interpolating in the low-dose region. In studies of exposed animal and human populations, the shape of a dose-response relationship at low doses may be practically impossible to ascertain statistically. This is because the population sample sizes required to estimate or test a small absolute cancer excess are extremely large; specifically, the required sample sizes are approximately inversely proportional to the square of the excess. For example, if the excess is truly proportional to dose, and if 1,000 exposed and 1,000 control persons are required in each group to test the cancer excess adequately at 100 rads, then about 100,000 in each group are required at 10 rads, and about 10,000,000 in each group are required at one rad. Thus, it appears that experimental evidence and theoretical considerations are more likely than empirical data to guide the choice of a dose-response function. In this dilemma and after much disagreement among some of its members, the present BEIR-III Committee

chose to adopt as a working model for low-LET radiation and carcinogenesis the linear-quadratic dose-response form with an exponential term to account for the frequently observed turndown of the curve in the high-dose region. However, in applying this multicomponent model, only certain of its derivatives, including the linear, linear-quadratic, and pure quadratic, could prove practical.

It should be remembered that in the 1972 BEIR-I Report<sup>2</sup> the cancer risk estimates for whole-body radiation exposure were derived from linear model average excess cancer risk per rad observed at doses generally of a hundred or more rads. These estimates have been generally criticized on the grounds that the increment in cancer risk per rad may well depend on dose and that the true risk at low doses may therefore be lower or higher than the linear model predicts.<sup>9</sup> In animal experiments, it has been shown, often with considerable statistical precision, that the dose-response curve for radiation-induced cancer can have a variety of shapes. As a general rule, the curve has a positive curvature for low-LET radiation, i.e., the slope of the curve increases with increasing dose. However, at high doses, the slope often decreases and may even become negative. Dose-response curves may also vary with the kind of cancer, with animal species, and with dose rate. On the basis of the experimental evidence and current microdosimetric theory, therefore, the present BEIR-III Committee could quite reasonably adopt as the basis for its consideration of dose-response models the linear-quadratic form with an exponential term for a negative slope in the high dose region.

On the other hand, the Committee recognized that for the most part, the available human data from the vast body of epidemiological studies fail to suggest any specific dose-response model, and are not sufficiently reliable

to discriminate among a priori models suggested by the experimental and theoretical work. However, there appears to be certain exceptions; for example, cancer of the skin is not observed at low radiation doses,<sup>17</sup> and dose-response relationships observed in the Nagasaki leukemia data appear to have positive curvature.<sup>18</sup> The incidence of breast cancer seems to be adequately described by a linear dose-response model<sup>11,19</sup> (Figure 3).

In attempts to apply derivatives of the multicomponent linear-quadratic model to the human data, simplification was required to obtain statistically stable risk estimates in many cases. It is now well known that members of the BEIR-III Committee were divided on this matter; some members of the Committee strongly favor the linear model, others favor the quadratic form. A further modification of the linear-quadratic form was assumed with the linear and quadratic components to be equivalent at some dose, which is consistent with epidemiological data and radiobiological evidence, and avoids dependence on either of the extreme forms.<sup>14,15</sup>

#### WHAT ARE THE UNCERTAINTIES IN ESTIMATION OF THE CARCINOGENIC RISK IN MAN OF LOW-LEVEL RADIATION?

The quantitative estimation of the carcinogenic risk of low-dose, low-LET radiation is subject to numerous uncertainties (Table 9). The greatest of these concerns the shape of the dose-response curve. Others include the length of the latent period, the RBE for fast neutrons and alpha radiation relative to gamma and x-radiation, the period during which the radiation risk is expressed, the model used in projecting risk beyond the period of observation, the effect of dose rate or dose fractionation, and the influence of differences in the natural incidence of specific types of cancer. In addition, uncertainties

are introduced by the biological risk characteristics of humans, e.g., the effect of age at irradiation, the influence of any disease for which the radiation was given therapeutically, and the influence of length of observation or follow-up. The collective influence of these uncertainties is such as to deny great credibility to any estimates of human cancer risk that can be made for low-dose, low-LET radiation. It is for these reasons, the present BEIR-III Committee has placed more emphasis on the methods of risk estimation than on any numerical estimates derived thereby.

#### WHAT ARE THE SOURCES OF EPIDEMIOLOGICAL DATA FOR THE ESTIMATION OF EXCESS CANCER RISK IN EXPOSED HUMAN POPULATIONS?

The tissues and organs involved in radiation-induced cancer in man about which we have the most reliable epidemiological data from a variety of sources from which corroborative risk estimates have been obtained include the bone marrow, the thyroid, the breast, and the lung. The data on bone and the digestive organs are, at best, preliminary, and do not approach the precision of the others. In several of these tissues and organs, risk estimates are obtained from very different epidemiological surveys, some followed for over 25 years, and with adequate control groups. There is impressive agreement when one considers the lack of precision inherent in the statistical analyses of the case-finding and cohort study populations, variability in ascertainment and clinical periods of observation, age, sex and racial structure, and different dose levels, and constraints on data from control groups.

By far, the most reliable and consistent data have been those of the risk of leukemia, which come from the Japanese A-bomb survivors,<sup>18</sup> the ankylosing

spondylitis patients treated with x-ray therapy in England and Wales,<sup>20,21</sup> the metropathia patients treated with radiotherapy for benign uterine bleeding,<sup>22</sup> and the tinea capitis patients treated with radiation for ringworm of the scalp<sup>23,24</sup> (Table 10). There is evidence of an age-dependence and a dose-dependence, a relatively short latent period of a matter of a few years, and a relatively short period of expression, some 10 years. This cancer is uniformly fatal.

The data available on thyroid cancer are more complex; the surveys include the large series of children treated to the neck and mediastinum for enlarged thymus,<sup>25</sup> children treated to the scalp for tinea capitis,<sup>23,24</sup> and the Japanese A-bomb survivors<sup>18</sup> and Marshall Islanders<sup>26</sup> exposed to nuclear explosions (Table 10). Here, there is an age-dependence and sex-dependence--children and females appear more sensitive. Although the induction rate is high, the latent period is relatively short, and it is probable that no increased risk will be found in future follow-up. In addition, most tumors are either thyroid nodules, or benign or treatable tumors, and only about 5 percent of the radiation-induced thyroid tumors are fatal.

In very recent years, much information has become available on radiation-induced breast cancer in women<sup>13,19</sup> (Table 11). The surveys include primarily women with tuberculosis who received frequent fluoroscopic examinations for artificial pneumothorax,<sup>27</sup> post-partum mastitis patients treated with radiotherapy,<sup>28</sup> and the Japanese A-bomb survivors in Hiroshima and Nagasaki.<sup>18</sup> Here, there is an age- and dose-dependency, as well as a sex-dependency, and the latent period is long, some 20 to 30 years. Perhaps about half of these neoplasms are fatal.

Another relatively sensitive tissue, and a complex one as regards



radiation dose involving parameters of the special physical and biological characteristics of the radiation quality, is the epithelial tissue of the bronchus and lung (Table 11). The information from the Japanese A-bomb survivors,<sup>18</sup> and uranium miners in the United States and Canada,<sup>29,30</sup> and the ankylosing spondylitis patients in England and Wales<sup>20,21</sup> provide reliable risk estimates of lung cancer exposed persons. There is some evidence of age-dependence from the Japanese experience and a relatively long latent period. This cancer is uniformly fatal.

The lifetime risk of radiation-induced bone sarcoma (Table 11), based primarily on radium and thorium patients who had received the radioactive substances for medical treatment, or ingested them in the course of their occupations<sup>31,32</sup> is low. For all other tumors arising in various organs and tissues of the body, values are extremely crude and preliminary estimates.

There is now a large amount of epidemiological information from various comprehensive surveys from a variety of sources; the most extensive, perhaps, include the Japanese A-bomb survivors,<sup>18</sup> the patients treated to the spine for ankylosing spondylitis,<sup>20,21</sup> the metropathia patients<sup>22</sup> and the early radiologists.<sup>33</sup> These data indicate that leukemia is now no longer the major cancer induced by radiation, and that solid cancers are exceeding the relative incidence of radiation leukemia by a factor as high as five<sup>5</sup>. That is, in view of the long latent periods for certain solid cancers to become manifest, it can be estimated that perhaps after some 30 years following radiation exposure, the risk of excess solid cancers may prove to be many times the risk of excess leukemia. These estimates remain very crude, since they do

not take into account the obvious lack of precision of certain of the epidemiological studies, particularly as regards radiation dose distribution, ascertainment, latency periods, and other important physical and biological parameters. The BEIR<sup>1,2</sup>, the UNSCEAR<sup>4,5</sup> and the ICRP<sup>6,7</sup> Reports have estimated the risk from whole-body exposure in different ways and based primarily on the studies of the Japanese A-bomb survivors<sup>8</sup>, and to a much lesser extent, from data on the ankylosing spondylitis patients,<sup>20,21</sup> the metropathia patients,<sup>22</sup> the tinea patients,<sup>23,24</sup> and similar epidemiological surveys carefully followed, many of which now have adequate control study populations, a very crude figure of the total lifetime excess absolute risk of radiation-induced cancer deaths can be derived. This figure for all malignancies from low-LET radiation, i.e., x-rays and gamma rays, delivered at low doses would be an overestimate of the true risk. The actual figure may be much lower in terms of excess cancer cases per million persons exposed per rad total lifetime risk, a large fraction of which would not necessarily be fatal.<sup>1,5</sup> Any such estimated figure remains very unreliable, but it does provide a very rough figure for comparison with other estimates of avoidable risks, or voluntary risks, encountered in everyday life.

#### WHAT ARE THE RISK ESTIMATES OF RADIATION-INDUCED CANCER IN MAN?

The chief sources of epidemiological data used in the current BEIR III Report<sup>1</sup> are the Japanese populations exposed to whole-body irradiation in Hiroshima and Nagasaki, patients with ankylosing spondylitis and other patients who were exposed to partial body irradiation therapeutically, or to diagnostic x-rays and various occupationally exposed populations, such as uranium miners and radium dial painters. Most epidemiological data do not systematically

cover the range of low to moderate radiation doses for which the Japanese atomic-bomb survivor data appear to be fairly reliable. Analysis in terms of dose-response therefore rely greatly on the Japanese data. The substantial neutron component of dose in Hiroshima and its correlation with gamma dose limit the value of the more numerous Hiroshima data to the estimation of cancer risk from low-LET radiation. The Nagasaki data, for which the neutron component of dose is small, are less reliable for doses below 100 rads.

For its illustrative computations of the lifetime risk from whole-body exposure, the present BEIR-III Committee chose three exposure situations for low-dose, low-LET radiation:

- (1) a single exposure of a representative (life-table) population to 10 rads;
- (2) a continuous, lifetime exposure of a representative (life-table) population to 1 rad per year; and
- (3) an exposure to 1 rad per year over several age intervals exemplifying conditions of occupational exposure.

The three exposure situations were not chosen to reflect any circumstances that would normally occur, but embrace the areas of concern--general population and occupational exposure and single and continuous exposure. These were substantially different from the exposure situation chosen for illustrative computation by the 1972 BEIR-I Committee, where 100 mrem per year was selected.

Below these dose levels chosen for the current report, the uncertainties of extrapolation of risk to very low levels were strongly felt by some members of the present Committee to be too great to justify risk estimation. The selected annual exposure, although only one-fifth the maximal permissible dose for occupational exposure, is nevertheless consistent with occupational

exposures in the nuclear industry. The U.S. 1969-1971 life-table was used as the basis for the calculations, and all results are expressed in terms of excess cancers per million persons throughout their lifetime after exposure. The expression time was taken as 25 years for leukemia and the remaining years of life for other cancers. Separate estimates were made for cancer mortality and for cancer incidence.

The resulting cancer mortality risk estimates for all forms of cancer differ by as much as an order of magnitude. The uncertainty derives chiefly from the range of dose-response models used, from the alternative absolute and relative projection models, and from the sampling variation in the source data. The lowest estimates are derived from the pure quadratic model; the highest, from the linear model. The linear-quadratic model provides estimates intermediate between these two extremes.

In the absence of any increased radiation exposure, among one million persons of life-table age and sex composition in the United States, about 164,000 persons would be expected to die from cancer, according to present cancer mortality rates. For a situation in which these one million persons are exposed to a single dose increment of 10 rads of low-LET radiation, the linear-quadratic model predicts increases of about 0.5% and 1.5% over the normal expectation of cancer mortality, according to the projection model.

For continuous lifetime exposure to 1 rad per year, the increase in cancer mortality, according to the linear-quadratic model, ranges from about 3% to 8% over the normal expectation, depending on the projection model.

To compare these estimates with those of the 1972 BEIR-I Report<sup>2</sup> and the 1977 UNSCEAR Report<sup>5</sup>, it was convenient to express them as cancer deaths

per million persons per rad of continuous lifetime exposure. For continuous lifetime exposure to 1 rad per year the linear-quadratic dose-response model for low-LET radiation yielded estimates some 25% to 50% below the comparable linear estimates in the 1972 BEIR-I Report<sup>2</sup>, depending on the projection model. Although the present BEIR-III Report<sup>1</sup> uses much more scientific information not available for the earlier 1972 report, the differences mainly reflect changes in the assumptions made by the two BEIR Committees almost a decade apart. The present Committee preferred a linear-quadratic, rather than linear, dose-response model for low-LET radiation, and preferred not to assume a fixed relationship between the effects of high-LET and low-LET radiation. The present risk estimates do not, as in the 1972 BEIR-I Report<sup>2</sup>, carry through to the end of life very high relative-risk coefficients obtained with respect to childhood cancers induced in utero by radiation. The present BEIR-III risk estimates do not differ appreciably from those in the 1977 UNSCEAR Report<sup>5</sup>.

Cancer-incidence risk estimates were less firm than mortality estimates. The present BEIR-III Committee used a variety of dose-response models and several data sources. The dose-response models produced estimates that differed by more than an order of magnitude, whereas the different data sources gave broadly similar results. For the linear-quadratic model and for continuous lifetime exposure to 1 rad per year, for example, the increased risks expressed as percent of the normal incidence of cancer in males were about 2% to 6%, depending on the projection model. Risks for females were substantially higher than those for males, due primarily to the relative importance of radiation-induced thyroid and breast cancer.

Estimates of excess risk for individual organs and tissues depend in



large part on partial-body irradiation and use a wider variety of data sources. Except for leukemia and bone cancer, estimates for individual sites of cancer were made only on the basis of the linear model and were stated in terms of excess cancer cases per year per million persons exposed per rad. For leukemia, the linear-quadratic model yielded about 1.0 to 1.4 excess leukemia cases (or deaths) per year per million persons exposed per rad, for females and males, respectively. For solid cancers, linear-model estimates were, for example: for thyroid in males, about 2, and in females, about 6; for female breast, about 6; and for lung, about 3.5 to 4. These risk coefficients derive largely from epidemiologic data in which exposure was at high doses, and these values may, in some cases, overestimate risk at low doses.

#### WHAT ARE THE IMPLICATIONS OF NUMERICAL RISK ESTIMATION FOR RADIATION PROTECTION AND PUBLIC HEALTH POLICY?

The present BEIR-III Committee has not highlighted any controversy over the health effects of low-level radiation. In its evaluation of the experimental data and epidemiological surveys, the Committee has carefully reviewed and assessed the value of all the available scientific evidence for estimating numerical risk coefficients for the health hazards to human populations exposed to low levels of ionizing radiation. Such devices require scientific judgment and assumptions based on the available data only, and has led to disagreement not only outside the committee room, but among committee members, as well. But such disagreement centers not on the scientific facts or the epidemiological data, but rather on the assumptions and interpretations of the available facts and data.

The present scientific evidence and the interpretation of available human data can draw very few firm conclusions on which to base scientific public health policy for protection standards for low-level radiation. However, based on the radiation risk estimates derived, any lack of precision does not minimize either the need for setting public health policy standards nor the conclusion that such risks are extremely small when compared with those available from alternative options, and those normally accepted by society as the hazards of everyday life. When compared with the benefits that society has established as goals derived from the necessary activities of energy production and medical care, it is apparent that society must establish appropriate standards and seek appropriate controlling procedures which continue to assure that its needs and services are being met with the lowest possible risks.

In a third of a century of inquiry, embodying among the most extensive and comprehensive scientific efforts on the health effects of an environmental agent, certain practical information necessary for determination of radiation protection standards for public health policy is still lacking, and may remain so. It is now assumed that exposure to radiation at low levels of dose carries some risk of deleterious effects. However, how low this level may be, or the probability, or magnitude of the risk, still are not known. Our best scientific knowledge and our best scientific advice are essential for the protection of the public health, for the effective application of new technologies in medicine and industry, and for guidance in the production of nuclear energy. Man cannot dispense with those activities which inevitably involve exposure to low levels of ionizing radiation in medicine, where he readily recognizes some degree of risk to health, however small, exists.

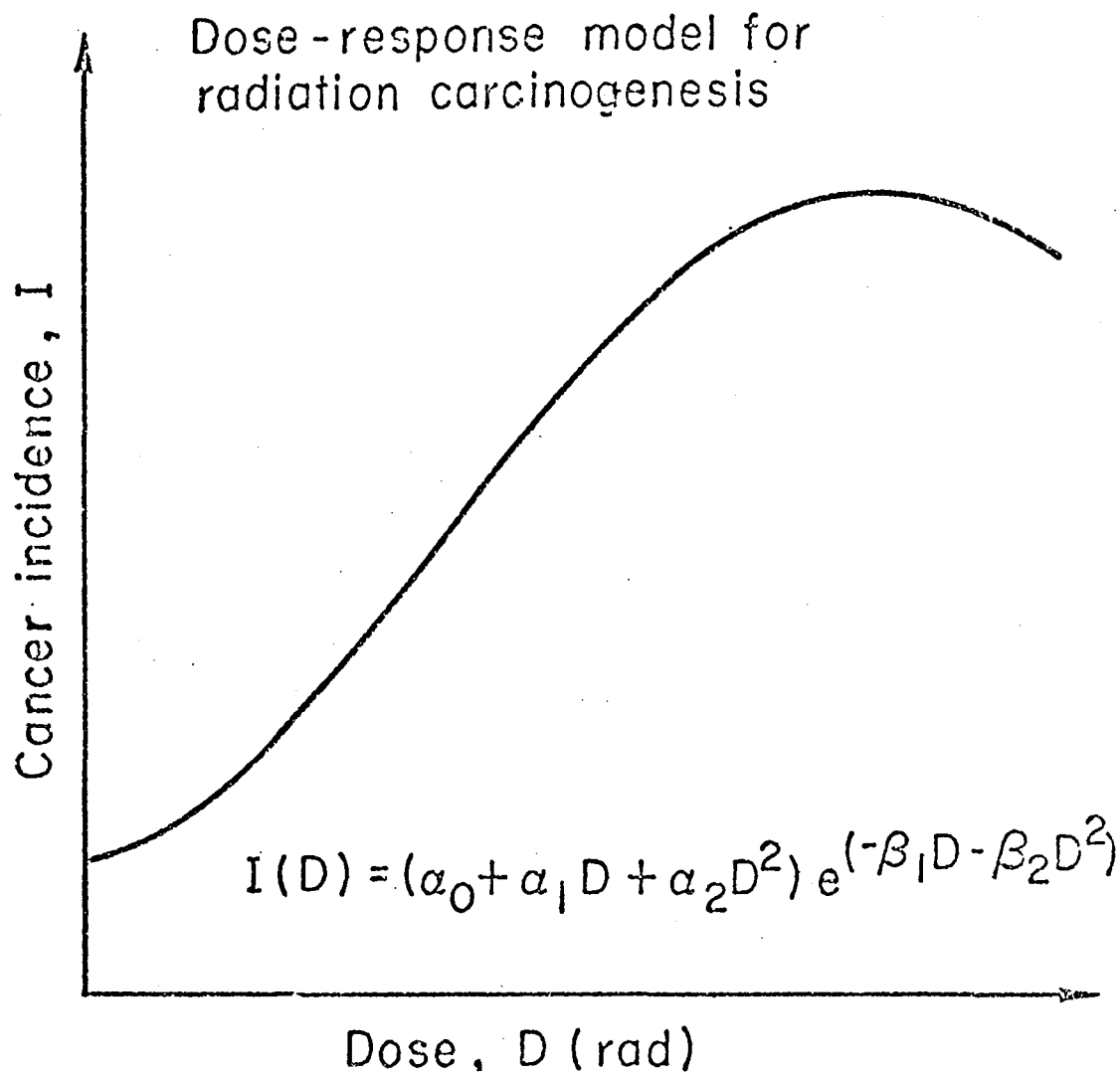
In the evaluation of such risks from radiation in all other societal activities involving ionizing radiation, including nuclear energy, as is done in medicine, it is also necessary to limit the radiation exposure to a level at which the risk is acceptable both to the individual and to society.

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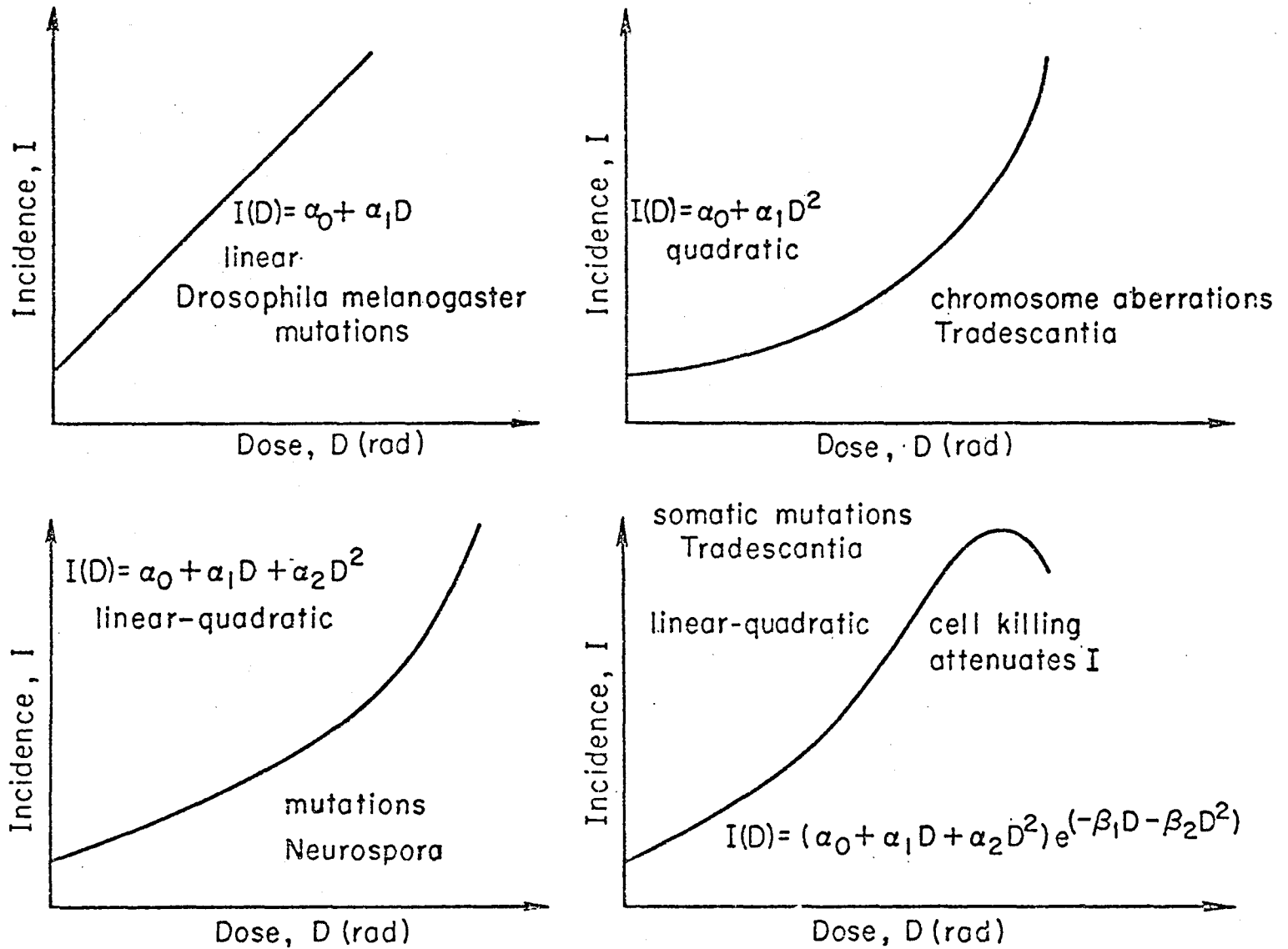
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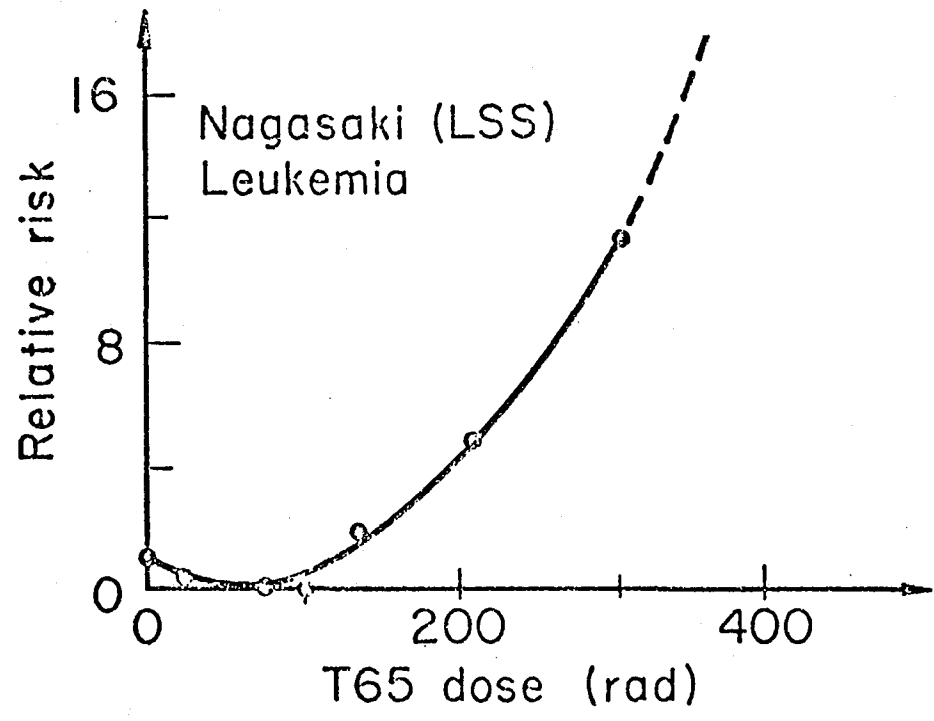
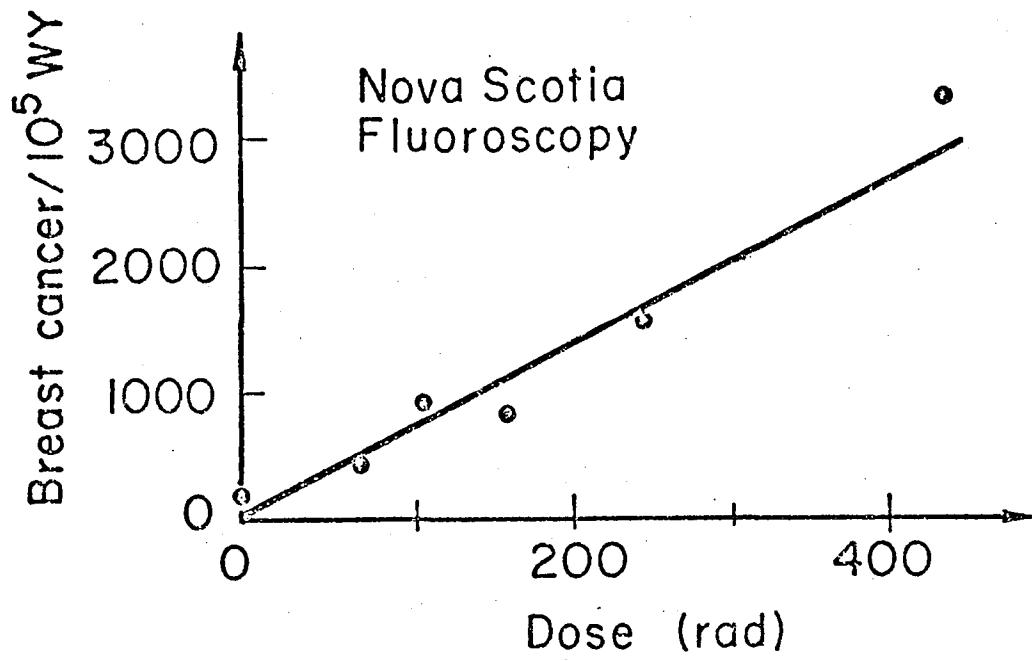
Figure 1

# SHAPES OF DOSE RESPONSE CURVES



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Figure 2



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Figure 3

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